The claimed invention is directed to a practical field of use and not merely to an abstract disembodied physical principle. For example, independent method claims 76 and 79 recite method operations and code to "identify one or more nucleotides, in the nucleotide sequence, that are to be varied or fixed in order to impart the desired activity." What could be more concrete, useful and tangible in a method or computer program product than identifying specific nucleotides in a sequence for fixing or varying. This is done "in order to impart a desired activity." Further, the claims act on data characterizing the protein variant library. And as recited a sequence activity model may be used to identify rank positions in a nucleotide sequence. All these things are very useful and certainly concrete and they relate to tangible subject matter: i.e., compositions of matter. Note that methods do not themselves have to recite steps that are somehow tangible. According to the PTO Guidelines,

> The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing.

While the claimed methods most certainly make use of theoretical concepts and mathematical manipulations, the end result is useful, concrete, and tangible. The claims recite a repeatable and predicable practical application of computational techniques. Nothing in the MPEP or Interim Guidelines suggests that a claim require more to be useful, concrete and tangible. See pages 20-22 of the Guidelines for a discussion of each the useful, concrete, and tangible criteria.

Withdrawal of the rejections under section 101 is respectfully requested. Note that claim 31 recites a method of actually "generating an optimized protein variant library." Certainly this claim meets any standard of Section 101.

The Rejections under 35 USC § 102

All claims were rejected as anticipated by US Patent Application 2001/0051855 naming Wang et al. as inventors. This patent application describes procedures for determining "structurally tolerant" residues in a sequence. Mutations of the structurally tolerant residues are relatively unlikely to produce inactive sequences during directed evolution procedures. The application proposes directed evolution techniques in which residues identified as structurally tolerant are selectively mutated. Various techniques are identified for identifying structurally tolerant residues. The principal technique involves calculation of a sequence's fitness based on its conformational energy. This approach is emphasized throughout the Wang et al. application

(see e.g., paragraphs 115 to 118) and is the basis for all examples presented in the application (see Section 6).

The disclosed conformational energy techniques do not develop "a sequence activity model" from "a training set of a protein variant library" (see operation (b) of claim 76). To the extent Wang et al. employ expressions that calculate conformational energy from sequence information, these expressions are not developed from *a training set*. Rather they are developed from purely *theoretical concepts* of rotamer interactions based on the relative positions of those rotamers in a backbone of a protein. Thus, to the extent that conformational energy based techniques are disclosed in the Wang et al. application, these techniques fail to disclose or suggest the developing a sequence activity model as recited in claim 76 or code for developing such model as recited in claim 79.

In other disclosed embodiments, the Wang et al. application employs the "site entropy" of individual residues in a sequence to identify structurally tolerant residues (see paragraphs 141 and 142).

To the extent that the site entropy equation is put forth as the "sequence activity model," one might argue that the database sequences considered by Wang et al. (sequences from GenBank etc. mentioned in paragraph 141) could be viewed as a "training set." However, the site entropy expression (see paragraphs 91-95) merely identifies residue positions that are represented by a large number of amino acids in a collection of related sequences. It does nothing else. It certainly does not itself predict "activity as a function of nucleotide types and corresponding position."

Applicants note that the Examiner cites paragraph 0023 as meeting the claim feature of "providing activity and nucleotide sequence information from each protein variant of *a training set*." This paragraph describes an iterative directed evolution technique in which improved mutants from one iteration are used as parent sequences in subsequent iterations. There is no suggestion that the improved mutants or any other sequences are somehow used as a training set. The discussion in paragraph 0023 is directed toward *in vitro* directed evolution techniques. Even if the paragraph was directed to computational techniques, there is nothing to suggest that the directed evolution results may be used to provide sequence and activity information for developing a sequence-activity model as claimed.

Applicants further note that the claim 76 also requires

> using the sequence activity model to rank positions in a nucleotide sequence and/or nucleotide types at specific positions in the nucleotide sequence in order of impact on the desired activity . . . .

According to the Examiner, this feature is found at paragraphs 0083 and 0084 of the Wang et al. patent application. Specifically, according to the Examiner, these paragraphs

> Teach quantifying the fitness (stability) of a sequence so that each amino acid will have a particular fitness value. Fitness is characterized as the extent to which a particular property (i.e. desired activity) of a polymer is optimized.

Paragraphs 0083 and 0084 describe use of the term "fitness" in the context of whole sequences, not individual amino acids or nucleotides. Therefore, these paragraphs cannot suggest a ranking of positions in a nucleotide sequence. Assuming for the sake of argument that the Wang et al. specification does describe quantifying fitness such that "each amino acid will have a particular fitness value" (as proposed by the Examiner), this still does not suggest ranking positions in a sequence "in order of impact on the desired activity."

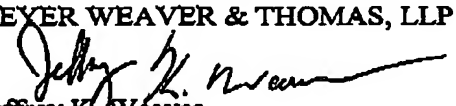
Because the methodology and algorithms described in the Wang et al. application fail to suggest a sequence activity model produced in the manner recited in the independent claims and for predicting activity as a function of nucleotide type and position, the Wang et al. application fails to anticipate the independent claims (claims 76 and 79) as well as any of the dependent claims (claims 77, 78, 80, and 81). Withdrawal of the art rejections is respectfully requested.

Conclusion

For the reasons set forth above, Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

If any fees are due in connection with the filing this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 500388 (Order No. MXGNP004X1).

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP



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